

U.S.S.N. 09/443,865

Filed: February 11, 2000

AMENDMENT AND RESPONSE TO OFFICE ACTION**Remarks**

Claim 41 has been rewritten in independent form. Claim 33 has been amended to correct an obvious typographical error. These amendments do not raise new issues and require no new search.

The present invention relates to the finding that the reduction by NQO2 of a prodrug, such as CB1954, to form a cytotoxic species is much more effective in the presence of NRH and analogues thereof.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 29, 31-33, 40, and 42-43 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 29 and 42 were rejected on the basis that the word "substituted" was indefinite. The use of the term "substituted" in a formula is well understood by those of ordinary skill in the art. The test for whether a claim is definite is whether or not one of ordinary skill in the art would understand the metes and bounds of the claims. In this case, any chemist would know exactly what was meant by the claim formula. Evidence is provided in the form of excerpts from Tabor's Medical Encyclopedia and a textbook on organic chemistry.

Rejection Under 35 U.S.C. § 103

Claims 29, 31-33, 40, and 42-44 were rejected under 35 U.S.C. § 103(a) as being unpatentable over *Biochem. Pharmacol.* 44(9) pages 1739-43, 1992, by Friedlos *et al.*

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("Friedlos1"), and *Biochem. Pharmacol.* 44(1), pages 25-31, 1992, by Friedlos *et al.*

("Friedlos2"), in view of *J. Biol. Chem.* 269(20), pages 14502-08, 1994, by Jaiswal ("Jaiswal").

Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) *the prior art suggests the claimed invention*; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

In this case, there is no suggestion of the claimed invention. The prior art relates to a *different protein - different amino acid, different biochemistry. NQO1 (DT-diaphorase) is not the same as, equal to or predictive of NQO2.*

The prior art must provide one of ordinary skill in the art with the motivation to make the proposed modifications needed to arrive at the claimed invention. *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lahu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application

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claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). This is not possible when the claimed invention achieves more than what any or all of the prior art references allegedly suggest, expressly or by reasonable implication.

There is no disclosure, suggestion or even hint in the cited art that one should substitute NQO2 (and substrate thereof) for NQO2.

There is no suggestion in any of the cited art that one could obtain much more effective formation of cytotoxic species in the presence of NRH.

The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). While the suggestion to combine may be found in explicit or implicit teachings within the references, from the ordinary knowledge of those skilled in the art, or from the nature of the problem to be solved, the "question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination. WMS Gaming, Inc. v International Game Technology, 184 F.3d 1339 at 1355 (Fed. Cir. 1999). "The range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999). Although with the answer in hand, the "solution" now appears obvious, that is not the test. The references must themselves lead those in the art to what is claimed. And in this case, there is simply no such teaching.

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There is nothing in Friedlos1, Friedlos2, or Jaiswal to indicate that NRH or 1-methylnicotinamide could be utilized by NQO2 to reduce CB10-200, let alone CB 1954, to more effectively form a cytotoxic species.

The stimulation of CB 1954 toxicity by NRH in human cells described in Friedlos1 is specifically ascribed to NQO1 (DT-diaphorase) *NOT* NQO2.

NQO2 and NQO1 are different proteins; they have different amino acid sequences and they have different biochemical properties.

There is nothing in Friedlos1, Friedlos2 or Jaiswal, alone or in combination, to indicate that NQO2 would have been at least as effective as NQO1 in the reduction of CB1954 in the presence of analogues of NRH. Hence, the claimed subject matter is not obvious.

The claimed method is based on the finding that the reduction by NQO2 of a prodrug, such as CB1954, to form a cytotoxic species is much more effective in the presence of NRH and analogues thereof. Without prior knowledge of this, there is no way in which the skilled person could have arrived at the claimed invention from Friedlos1, Friedlos2 or Jaiswal. Only with *hindsight*, could the examiner argue that it is obvious to go from a disclosure relating to NQO1 to NQO2.